Effects of DW-286a, a fluoroquinolone antibiotic agent, on hERG channel currents expressed in CHO cells

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Prolongation of the QT interval may result in a potentially dangerous arrhythmia. The most commonly proposed mechanism for QT interval prolongation (LQT) by pharmaceuticals is inhibition of the rapid delayed rectifier potassium channel (IKr). The LQT potency of pharmaceuticals can be effectively evaluated by examining the effect on human ether-a go-go-related gene (hERG) channels expressed in CHO cells, known to be equal to IKr. We have transfected hERG into CHO cell lines transiently to express high levels of functional hERG channels. Western blot analysis showed one protein band (130 ~ 150 kDa). We used these cells to evaluate LQT potency of DW-286a at 30°C. Recently DW-286a, a fluoroquinolone antibiotic agent with the formula (7-(4-Aminomethyl-3-methoxyimino-4-methylpyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid hydrochloride), has been developed by Dong-Wha Pharmaceutical INC. (Anyang, Korea) for the treatment of both gram-positive and gram-negative bacterial infections. DW-286a decreased hERG channel currents in a dose-dependent manner with an estimated IC50 of 83.59±7.36 mM. But, the blockade of DW-286a on hERG channel was slight as compared with other fluoroquinolone antibiotic agents (ex. IC50 of sparflaxacin; about 34 mM)

Studies of the agonist-induced receptor sequestration of dopamine D2 receptor

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The dopamine D2 receptor (D2R) is target for antipsychotic drugs and associated with several neuropsychiatric disorders. The internalization (sequestration) of G protein-coupled receptor is caused by agonist-induced receptor phosphorylation mediated by GRK, followed by the interaction with β-arrestin. In this study, we examined the agonist-dependent sequestration/internalization of dopamine D2R, which were transiently expressed in HEK 293 cells with or without GRK co-expression. Co-expression of GRK2 or GRK3 markedly enhanced the sequestration of D2R. GRK-dependent sequestration of D2R was regulated by the interaction with D1R and by protein kinase C.

The mechanism of sphingosine-1-phosphate induced contraction in cat esophageal smooth muscle cells.

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We previously shown that sphingosylphosphorylcholine, a lysophosphatidic acid, produced contraction in isolated single cells of cat ilium. We investigated the mechanism of sphingosine-1-phosphate (S1P)-induced contraction of circular smooth muscle cells in cat esophagus. S1P produced esophageal contraction in a dose dependent manner. The maximal contraction (10^{-5}M) induced at 1min. Pertussis toxin (PTX) inhibited contraction induced by S1P, suggesting that the contraction is mediated to a PTX-sensitive G-protein. Among the phospholipase inhibitors, U73122 reduced the contraction. To evaluate the role of PKC, GF109203X or chelerythrine was pretreated prior to S1P, and this contraction was decreased by either inhibitor. MAPK kinase inhibitor PD98059 blocked the contraction significantly, but p38 mitogen-activated protein kinase (MAPK) inhibitor SB202190 did not. However, cotreatment of PD98059 and chelerythrine showed no significant difference when compared with alone treatment of this inhibitors. Western blotting revealed that G-protein coupled endothelial differentiation gene